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December 22, 2000

Dockets Management Branch
Food and Drug Administration
(HFD-7)
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Digoxin Products for Oral Use: Revocation of Conditions for Marketing

Dear Sir/Madame:

Attached are the comments of my client Jerome Stevens Pharmaceuticals (JSP), a manufacturer of digoxin tablets for oral use. As you are aware, FDA recently settled a lawsuit brought by Bertek and Amide Pharmaceuticals against the agency and agreed to revoke 21 CFR §310.500. That regulation allowed digoxin, a DESI drug, to remain on the market for nearly 25 years without requiring an NDA or ANDA as long as lots were tested and certified by FDA. Bertek and Amide obtained premarket approval in an attempt to gain competitive advantage. They then sued FDA to force the agency to require removal of any company that had not sought or received comparable regulatory approval. FDA quickly acquiesced to this request. FDA immediately published a proposed rule seeking to revoke §310.500 and remove from the market any digoxin product for which a NDA or ANDA had not been approved within 30 days of a final rule.

In the event that FDA goes forward with a final rule, which we believe is unjustified by the administrative record, we request that the period for submission and review of a premarket approval application be at least 2 years. That time period has been used in other analogous cases involving DESI drugs. Equity, fairness, and the need for the agency to preserve competitive neutrality require it.

In addition to your review of our comments attached, we respectfully request a meeting to discuss this matter further. We will observe the limits on exparte meetings in the context of notice and comment rulemaking. The speed with which this matter has moved, however, makes it clear to us that the agency has already had extensive discussions with Bertek and Amide, and/or their parents without any discussion with us. I will call you next week to schedule a convenient time for JSP to meet with the appropriate agency representatives.

Thank you for your consideration of this matter. Please call me with any questions or if I may be of assistance.

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Best regards.

Sincerely,

Marc J. Scheinbaum

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COMMENTS OF JEROME STEVENS PHARMACEUTICALS, INC.
TO THE
U.S. FOOD AND DRUG ADMINISTRATION
ON
DIGOXIN PRODUCTS FOR ORAL USE;
REVOCATION OF CONDITIONS FOR MARKETING
[DOCKET NO. 00N-1610] (Proposed Rule);
DIGOXIN PRODUCTS FOR ORAL USE; REAFFIRMATION OF
NEW DRUG STATUS AND CONDITIONS FOR MARKETING
[Docket No. 00N-1609] (Notice).

December 22, 2000

Jerome Stevens Pharmaceuticals, Inc. (JSP) respectfully submits these comments in response to the above referenced proposed rule and notice, which appeared in the *Federal Register* on November 24, 2000. JSP urges the Food and Drug Administration (FDA) to reconsider its proposal to revoke 21 C.F.R. § 310.500 setting marketing conditions for digoxin drug products. In the event that the agency proceeds with the rulemaking, **FDA must extend the effective date of the proposed rule to provide sufficient time for affected manufacturers to prepare required regulatory filings, and for FDA to properly review those filings.**

I. Product Background

A. Product and Indications

JSP is a manufacturer of digoxin products for oral use. Its digoxin products comply fully with the regulatory requirements of § 310.500. They have been on the market since 1995 as a safe, effective and cost-saving alternative to consumers.

Digoxin is a member of the group of cardiac drugs known as cardiac glycosides. It was reportedly discovered and developed in 1930, and has been marketed in the United States since 1934. It is labeled for use in heart failure, atrial fibrillation, atrial flutter, and paroxysmal atrial tachycardia. Digoxin is available for oral and intravenous administration.

B. Regulatory Background

Marketing of digoxin pre-dated the Federal Food, Drug and Cosmetic Act (FDCA), 21 U.S.C. § 201 *et seq.* Over the years, as part of its Drug Efficacy Study Implementation (DESI) program, FDA classified many "grandfathered" drugs as new drugs requiring approval by the agency to remain on the market. In most cases, the agency required manufacturers to submit new drug applications (NDAs), or abbreviated

new drug applications (ANDAs), for the grandfathered products determined to be new drugs. In the case of digoxin tablets, FDA adopted a different regulatory approach.[1]

In 1970, FDA instituted a voluntary certification program in which participating manufacturers agreed not to release new lots of digoxin tablets until samples of the lots were tested by FDA and found to meet the requirements of the United States Pharmacopoeia (USP) for potency and content uniformity. Due to agency concerns over differences in bioavailability between batches made by different manufacturers, and even among some batches made by the same manufacturer, the USP monograph was revised to include a requirement for dissolution, which correlates with bioavailability.

On January 22, 1974, the *Federal Register* contained an FDA notice announcing its determination that digoxin products for oral use (tablets and elixir) constitute new drugs under the FDCA (39 *Fed. Reg.* 2471). FDA issued a proposed regulation establishing conditions for marketing the products. The regulation, § 310.500, included the following requirements: (1) a mandatory FDA certification program for digoxin tablets based on dissolution testing by the National Center for Drug Analysis; (2) mandatory recall of any previously marketed batch of digoxin tablets found to fail USP dissolution specifications; (3) submission of ANDA's and bioavailability tests for oral digoxin products; and (4) labeling requirements for oral digoxin products. In response to comments received on the proposed rule, FDA published notices in the *Federal Register* that stayed the requirements for submission of ANDAs and product labeling. 39 *Fed. Reg.* 9184 and 9219 (March 8, 1974). The stay on labeling was later lifted, and the regulation was amended to include a set of new labeling conditions. 41 *Fed. Reg.* 43135 (Sept. 30, 1976). Product sponsors have manufactured and safely sold digoxin under the regulatory regime described above for almost 25 years.

C. Legal Action Against FDA

In September 1993, Glaxo Wellcome submitted an NDA for Lanoxin (digoxin) tablets. The filing contained published studies and new clinical investigations sponsored by Glaxo Wellcome. On September 30, 1997, FDA approved the Lanoxin tablets NDA for treatment of heart failure and atrial fibrillation. On December 23, 1999, FDA approved an ANDA filed by Amide Pharmaceuticals, Inc. for Digitek® (digoxin) tablets.

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[1] Digoxin products for parenteral use and digoxin solution in capsules have been classified as new drugs.

With its ANDA approved, Amide and its distributor, Bertek Pharmaceuticals, Inc., filed suit against FDA seeking an injunction to require the agency to prohibit further marketing of digoxin products pursuant to § 310.500. *Bertek Pharmaceuticals, Inc. and Amide Pharmaceuticals, Inc. v. Henney*, Civ. Action No. 1:00CV02393 (Oct. 4, 2000). That action was likely taken primarily in an attempt to limit competition and increase its own market share. The Complaint asserted that because FDA had deemed digoxin products new drugs in 1974, its decision to permit their marketing pursuant to the certification program under § 310.500, without an NDA or ANDA, violated the FDCA. Moreover, the subsequent NDA approval of digoxin products for oral use obviated FDA's need to maintain the certification program to keep the drug on the market. In essence, the plaintiff asserted that once a digoxin product received approval through the NDA and ANDA process, the provisions of § 310.500 were somehow rendered obsolete and unsafe, and thus illegal.

FDA did not file an Answer to the October 4, 2000 Complaint. It chose instead to agree immediately with the plaintiff's claim. With unprecedented speed, indicating a prior understanding with the Bertek and Amide, on November 17, 2000, the Government joined the plaintiffs in agreeing to a Declaratory Judgement against it that required elimination of the digoxin regulation. On November 24, 2000, FDA published a notice in the *Federal Register* reaffirming that digoxin products for oral use are new drugs, and issued a proposed rule to revoke § 310.500.

II. FDA Should Not Set Regulatory Policy To Avoid Litigation

An agency's rulemaking power is constrained by statute. It is not to be exercised arbitrarily or capriciously. An agency must review the available evidence and articulate a reasoned basis for rules. *See, e.g., Motor Vehicle Manufacturers Ass'n v. State Farm Mutual Auto Insurance Co.*, 463 U.S. 29, 43 (1983); *NRDC v. EPA*, 822 F.2d 104 (D.C. Cir. 1987). This fundamental principle of administrative law is particularly cogent in the case of FDA, a public health agency charged with applying scientific expertise. FDA rulemaking must be premised on a demonstrable public health purpose, and supported by scientific principle. The proposed rule fails to meet this standard.

The Department of Justice (DOJ) reportedly settled the case immediately by agreeing to the plaintiffs' demands at the request of FDA. That action was curious given FDA's clear authority to promulgate a regulation in the form of §310.500, and DOJ's winning track record in defending that authority under the *Heckler v. Chaney* line of cases (470 U.S. 821 (1985)). In *Chaney*, the U.S. Supreme Court ruled that FDA has discretion in implementing the FDCA that is not reviewable by the courts under the Administrative Procedure Act.

At no point in this speedy notice and comment rulemaking does FDA identify any threat to public health that has arisen from the operation of § 310.500 or inability to adequately protect the public interest. The only ostensible risk posed by digoxin is the potential for differences in bioavailability among batches (as true for the Bertek and Amide products as well as the JSP products). 65 *Fed. Reg.* at 70573. Yet the certification requirements and dissolution testing imposed by § 310.500 were designed to address that risk. FDA offered no evidence in the preamble to the proposed rule that existing procedures failed to address that issue adequately. There is no review of the history of the program, of the science underlying the certification procedure, or of purported shortcomings in its implementation.

Not only does FDA fail to consider the overall integrity of the certification procedure, or its authority to impose it for DESI drugs, there is also no analysis of its specific application. The preamble does not identify a single adverse event related to digoxin since § 310.500 became effective, much less one related to differences in bioavailability. Indeed, the preamble fails to express any quantifiable concern that the current certification system is inadequate, poses any threat or has resulted in any harm to the public health. In the absence of such a public health justification for revoking the regulation, it is difficult to understand the basis for the agency's action -- other than to avoid the expenditure of resources required to defend the *Bertek* suit.

Finally, the agency does itself a severe disservice by appearing to quickly cave-in to the request of industry plaintiffs in order to settle a lawsuit. Experienced litigators understand that surrendering to litigation breeds much more litigation. The message to its outside constituencies from this action is that suing the agency can be a successful tactic to gain an immediate decision favorable to the industry plaintiffs. This is especially offensive and unwise in this case where the rationale behind the Bertek lawsuit was so clearly an effort to gain competitive advantage in the marketplace and not any demonstrated need to protect the public health.

FDA must remain competitively neutral. The agency's resolve must not appear to sway based on the force applied by any particular company or trial attorney. If the agency believes, as it appeared to have believed for 25 years, that the certification system was adequate to protect the public health, this proposed rule must be withdrawn. If the existing rule is no longer adequate, FDA owes other regulated companies and the public a complete and candid description of the changing facts or circumstances that justify new regulation. If it cannot fairly and truthfully identify a meaningful public health rationale served by revocation of § 310.500, the agency should withdraw the proposed rule.

III. Any Final Rule Must Provide Adequate Time to Prepare the Required Submissions and for FDA Review

In the event that FDA does articulate a real and meaningful public health rationale for the revocation of § 310.500, it must extend the effective date of the final rule that is issued. The agency must allow a reasonable period of time for those manufacturers, including JSP, which currently produce and market digoxin products pursuant to the § 310.500 certification program. This time must be sufficient to prepare, submit, and obtain FDA review and approval for an NDA or ANDA. The proposed deadline of 30 days is grossly insufficient. Given the totality of the circumstances where FDA appears to be siding with particular companies seeking competitive advantage, it would be particularly onerous and unfair to pressure other companies out of the marketplace because they couldn't conduct equivalency testing and prepare premarket applications that must then be reviewed and approved by FDA, all within the 30 day time period proposed for the final rule.

The Bertek lawsuit was settled by FDA in slightly less than one month after its filing. The suit was filed on October 4, 2000 and Declaratory Judgement was entered on November 20, 2000. The notice and a new proposed rule appeared in the *Federal Register* only four days after the court's judgement, on November 24, 2000, with comments due within 60 days. Approved NDAs or ANDAs were required for a product to remain on the market within 30 days after the rule becomes final. How fast is this railroad going to run? It would be an outrageous abuse of FDA's governing laws if after 25 years where FDA preapproval was not required for digoxin, the time period for complying with these new requirements were not extended for a reasonable period of time. As described below, that time period has traditionally been 3 years in analogous cases.

Further, I cannot remember any time where a new proposed rule was actually published within four days of a court settlement, or within 50 days of the initiation of an industry lawsuit. FDA's policy and legal personnel are becoming amazingly efficient given all the steps that must be taken to effectuate notice and comment rulemaking. In the alternative, and more likely, the Bertek lawsuit represented a contrived understanding at many levels within FDA that the agency opposed the existing rule and required a catalyst for its repeal. Since JSP as an affected party was not provided the opportunity for any input before the "die was cast," the company must, in all fairness, be given adequate time to comply. Action otherwise would constitute the worst type of arbitrary, capricious and abuse of the agency's discretion. JSP would seek to protect its legal and constitutional rights in such circumstance. We would recommend initiation of litigation immediately, especially given the agency's demonstrated willingness to settle such actions so efficiently.

submission of a complete validation report, JSP was released from batch-to-batch certification requirements. There have been no serious adverse events associated with its digoxin products. Yet if the proposed rule becomes final and goes into effect within thirty days, JSP will be forced to halt production. The Company will not be able to conduct acceptable equivalency testing and prepare an approvable NDA or ANDA within 30 days' time. Moreover, even if that were possible, FDA could not review and approve the submission within such a short time frame.

As FDA itself notes in the preamble to the proposed rule, there are presently three manufacturers of digoxin tablets. Two of them (Glaxo Wellcome and Bertek) have already obtained an NDA or ANDA. If FDA revokes § 310.500 effective 30 days from the date of publication, it will remove JSP from the market. Competition among the three manufacturers is already quite intense. The two competitor companies will quickly fill the gap created by JSP's absence. JSP will then face severe difficulty re-entering the market and re-establishing its position after an absence which could span a year or more while waiting for FDA to approve an NDA or ANDA. Consumers would likely be forced to pay higher prices due to the loss of a generic competitor with a significant market position. The potential financial loss to JSP from the disappearance of this product line would be substantial. In these circumstances, such loss could constitute a government "taking" for which the federal government could be financially responsible. In light of the apparent lack of risk to the public health from the manufacture of digoxin pursuant to § 310.500, we hope you will be reasonable in providing a sufficient period in which JSP can prepare an NDA or ANDA for your review.

Moreover, FDA's decision to revoke the rule in such short order presents an important public health concern. The abrupt disappearance of one of only three manufacturers of an important cardiac drug could disrupt supply. The proposed rule contains no discussion of whether, or how 15-20 percent of the market can be serviced if the final rule eliminates this source of supply. Absent consideration of this issue, and the others highlighted above, it is difficult to envision how FDA can finalize a rule in its proposed form.

FDA's own recent regulatory history offers a clear precedent for setting an effective date that provides sufficient time for compliance with the new NDA or ANDA requirement. On August 14, 1997, for example, FDA announced in a *Federal Register* notice that, as part of the DESI program, levothyroxine sodium, a "public health risk," was deemed a new drug and must comply with the NDA approval requirements. 62 *Fed. Reg.* 43535 (Aug. 14, 1997). The agency set an effective date of three years from publication of the final rule for manufacturers to comply, until August 2000. It then extended the deadline one additional year, until August 2001, to ensure the opportunity

for compliance, despite knowledge that an NDA submitted by JSP would be approved by the original date.

The levothyroxine sodium rulemaking is strikingly similar to the digoxin matter. Levothyroxine was introduced into the market as a prescription drug prior to 1962, before NDAs were required. As in the case of the digoxin proposed rule, FDA based its decision on concerns over potential inconsistencies in the potency and bioavailability of the products' active ingredient.[2] Despite its stated concern over the potential safety risks presented by levothyroxine sodium products, FDA gave manufacturers 3 years -- until August 14, 2000 -- to file and obtain approval of NDAs.

Moreover, when it appeared to FDA that levothyroxine sodium manufacturers might not meet the deadline for the effective date, the agency extended the deadline for a fourth year despite determining that inconsistent potencies of the drug constituted "a public health risk." On April 26, 2000, FDA published a notice in the *Federal Register* extending the time for filing and obtaining approval of NDAs by one additional year to August 14, 2001. 65 *Fed. Reg.* 24488 (April 26, 2000). It did so even though one manufacturer -- JSP -- had already submitted an NDA and was near approval.[3] The basis for the extension was "to allow sufficient time for manufacturers to conduct the required studies and to prepare and submit applications, as well as to allow the agency sufficient time to review these applications." 65 *Fed. Reg.* at 24489. The additional time, in FDA's view, would insure that the supply of this medically necessary product would not be disrupted. FDA should demonstrate similar flexibility for manufacturers of digoxin.

Digoxin is a medically necessary product, used to treat serious cardiac conditions. JSP supplies approximately 15-20 percent of the drug nationally. Yet FDA appears to have given no consideration as to whether closing one of only three manufacturers could disrupt supply and increase consumer cost. The preamble to the proposed rule makes no mention of these important public health considerations. Nor

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[2] Unlike the current rulemaking, FDA identified in the preamble to the levothyroxine sodium rule possible shortcomings in the existing regulatory requirements, including numerous instances of inadequate stability testing which resulted in uneven product potency and unreliable expiration dates. Moreover, the agency described reported incidents of adverse events due to subpotent or superpotent LS products. It also referenced concerns over changes in product formulations that were not reviewed by FDA that resulted in unexpected increased potency.

[3] JSP received approval for its NDA No. 21-210 **on August 21, 2000.**

does FDA appear to have consulted with JSP or any other industry representative regarding the length of time that would be necessary to prepare and obtain approval for an NDA or ANDA.

In the case of levothyroxine sodium, FDA identified specific threats: fifty-eight adverse drug events associated with levothyroxine sodium, which specifically arose from issues of variable potency; ten firm-initiated recalls due to stability problems; and unapproved formulation changes. 62 *Fed. Reg.* at 43536. Digoxin, by contrast, has not been associated with demonstrable risks, and presents little urgency. As noted above, FDA has identified no adverse events associated with the product as manufactured under the certification system, much less any harm related to variable potency. The

FDA should set an effective date that provides JSP and other manufacturers which may choose to enter the field, with an appropriate period of time to comply with the new premarket approval requirements. JSP estimates that the preparation of an ANDA, along with the review by FDA and the necessary adjustments to the application or manufacturing practices, will take a minimum of three years to complete. That was the time accorded to sponsors of levothyroxine sodium. The final rule should provide comparable time for the completion and review of digoxin NDAs or ANDAs.

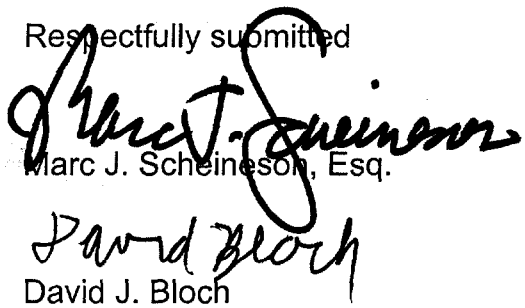
IV. Conclusion

JSP urges FDA to adequately consider all factual and scientific circumstances. Until it identifies real shortcomings with the certification and dissolution testing system established by § 310.500, there is little impetus to revoke the rule. As you know best, rulemaking requires a supportive administrative record independent from any settlement FDA may have reached with Bertek and Amide. In the event that FDA identifies such evidence, and chooses to proceed with its announced revocation of § 310.500, it must establish an effective date for the final rule that allows sufficient time for manufacturers to prepare, submit and gain approval for a NDA or ANDA. That time period should be consistent with analogous factual situations. We believe the Levothyroxine sodium situation, in which JSP is also involved, is a properly analogous situation. You may know of many others. Therefore, we respectfully request a period of at least two years from the date the proposed digoxin rule becomes final before a NDA or ANDA has to be approved to continue to market the drug. FDA should consult with industry and its own reviewers to determine a realistic timeframe.

JSP seeks consistent agency policy which is its right and FDA's statutory responsibility. FDA must demonstrate flexibility in its revision of the regulation of

digoxin similar to that which it applied in its revision of the regulation of levothyroxine sodium.

Respectfully submitted



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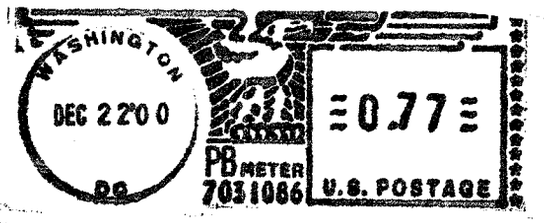

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